Poster 8521

First-line datopotamab deruxtecan (Dato-DXd) + rilvegostomig in advanced or metastatic non-small cell lung cancer: Results from TROPION-Lung04 (cohort 5)

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Objective

- TROPION-Lung04 (NCT04612751) is investigating the safety and efficacy of Dato-DXd in combination with different immunotherapy agents ± carboplatin. Here we present the results from cohort 5 which assessed Dato-DXd, an antibody-drug conjugate, administered in combination with rilvegostomig, a bispecific antibody.

Conclusions

- The safety profile for the combination of Dato-DXd and rilvegostomig was consistent with the known safety profiles of each individual agent, and no new safety signals were reported.
- The combination of Dato-DXd and rilvegostomig showed encouraging activity as first-line treatment for patients with advanced or metastatic NSCLC without AGAs.
  - Responses were observed in patients with both squamous and non-squamous histologies regardless of PD-L1 expression levels.
- At data cutoff, time to event data (DoR and PFS) were considered immature.

Plain language summary

Why did we perform this research?

- For patients with non-small cell lung cancer (NSCLC) that has spread to nearby tissue or lymph nodes (advanced) or to other parts of the body from its original site (metastatic) and that has no specific genetic components that can be targeted (actionable genomic alterations, AGAs), the standard treatment is a type of drug that blocks the PD-L1 or PD-1 protein to help the immune system kill cancer cells (PD-[L]1 inhibitors) combined with chemotherapy.[1,2] However, not all patients respond to this treatment.[3]
- Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate that consists of an antibody and an anticancer drug, joined via a stable linker.[4] Dato-DXd has shown efficacy in patients with advanced or metastatic NSCLC when given on its own or when combined with PD-(L)1 inhibitors.[5–7]
- Rilvegostomig is a drug that blocks proteins called PD-1 and TIGIT on the surface of immune cells, which helps the immune system kill cancer cells.[8] Rilvegostomig has shown encouraging activity in patients with advanced NSCLC.[8]
- Researchers would like to know if Dato-DXd combined with rilvegostomig could improve antitumor responses compared with PD-(L)1 inhibitors.
- The TROPION-Lung04 study was designed to investigate Dato-DXd in combination with different anticancer drugs, with or without chemotherapy, in patients with advanced or metastatic NSCLC without AGAs. Here we report the results from cohort 5, in which patients received treatment with Dato-DXd in combination with rilvegostomig.

How did we perform this research?

- Forty eligible patients, who had not previously received treatment, received Dato-DXd + rilvegostomig every 3 weeks. Each patient continued treatment until their cancer started growing or side effects became unacceptable.

What were the findings of this research?

- The safety of Dato-DXd plus rilvegostomig was manageable and no new side effects were seen.
- The percentage of patients who had a decrease in the size or number of tumors after treatment was 58% (objective response rate, ORR), and the percentage of patients whose tumors shrank or remained stable was 95% (disease control rate, DCR).

What are the implications of this research?

- Patients with advanced or metastatic NSCLC do not all respond to the current standard of care; the combination of Dato-DXd and rilvegostomig could provide a promising, alternative treatment option for this patient population.

Where can I access more information?

- For more information about TROPION-Lung04, please visit https://clinicaltrials.gov/study/NCT04612751. You may also speak to your doctor about clinical studies.

1. Hendriks LE, et al. Ann Oncol 2023;34:358–76; 2. Leighl N, et al. JCO 2025;43:e17-e30; 3. Chen S, et al. Front Oncol 2021;11:562315; 4. Okajima D, et al. Mol Cancer Ther 2021;20:2329–40; 5. Ahn M-J, et al. J Clin Oncol 2025;43:260–72; 6. Levy BP, et al. J Clin Oncol 2024;42:(suppl 16):abstr 8617; 7. Cuppens K, et al. ESMO Open;10:104164; 8. Hiltermann TJN, et al. J Thorac Oncol 2024;19:S33.

This study (NCT04612751) was sponsored by AstraZeneca. In July 2020, Daiichi Sankyo entered into a global development and commercialization collaboration agreement with AstraZeneca for datopotamab deruxtecan (Dato-DXd).
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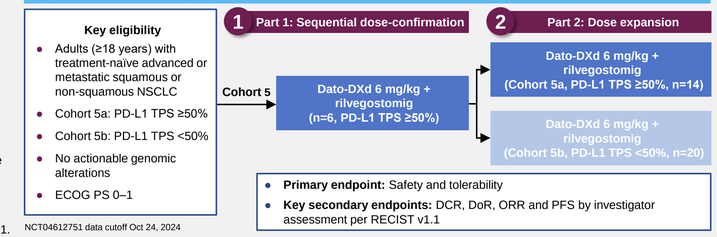
Introduction

- First-line anti–PD-(L)1 agents ± chemotherapy are the standard of care for 1L treatment of patients with advanced or metastatic NSCLC without AGAs;[1,2] however, not all patients respond to treatment.[3]
- Dato-DXd, a TROP2-directed ADC,[4] has shown efficacy and acceptable tolerability in patients with advanced or metastatic NSCLC as monotherapy or when combined with PD-(L)1 inhibitors.[5-7]
- In the phase 1/2, open-label, multicenter, dose-escalation and expansion study, ARTEMIDE-01, rilvegostomig, an Fc-reduced, monovalent, bispecific humanized IgG1 monoclonal antibody targeting PD-1 and TIGIT, demonstrated encouraging preliminary efficacy and was well tolerated in patients with checkpoint inhibitor-naïve advanced NSCLC, with PD-L1 TPS of ≥1%.[8]
- The combination of Dato-DXd and rilvegostomig may therefore have the potential to enhance antitumor responses versus anti–PD-(L)1 inhibitors alone.
- TROPION-Lung04 is investigating Dato-DXd and different immunotherapy agents ± carboplatin; here, we report safety and preliminary efficacy for patients who received first-line Dato-DXd + rilvegostomig in cohort 5 of the TROPION-Lung04 study.

Methods

- TROPION-Lung04 is a phase 1b, open-label, dose-escalation/confirmation and expansion study. Cohort 5 is enrolling patients with advanced or metastatic NSCLC, without AGAs, with PD-L1 TPS ≥50% or <50%.
- The dose-confirmation part of the study was designed using the mTPI-2 method.
- In cohort 5, treatment-naïve patients received Dato-DXd (6 mg/kg) + rilvegostomig:
  - Cohort 5a: PD-L1 TPS ≥50% (n=20)
  - Cohort 5b: PD-L1 TPS <50% (n=20)
- Patients received treatment until disease progression, unacceptable toxicity, or other discontinuation criteria were met.
- The primary endpoint of this study was safety and tolerability, including DLTs, TEAEs and other safety parameters.
- Secondary endpoints included ORR, DoR and PFS per RECIST v1.1.

Figure 1. TROPION-Lung 04 study design



NCT04612751 data cutoff Oct 24, 2024

Results

Patients

- Overall, 40 patients (Cohort 5a, n=20; Cohort 5b, n=20) had received Dato-DXd + rilvegostomig at data cut-off (October 24, 2024); Dato-DXd treatment was ongoing in 19 patients and rilvegostomig treatment was ongoing in 20 patients. Median follow-up was 5.60 (0.1–18.3) months.
- Baseline patient demographics and disease characteristics are shown in **Table 1**.

Table 1. Patient demographics and disease characteristics at baseline

		Dato-DXd + rilvegostomig N=40
Age, median (range), years		67.5 (44.0–80.0)
Male, n (%)		26 (65.0)
Race, n (%)	White Asian Black/African American	32 (80.0) 7 (17.5) 1 (2.5)
Histology, n (%)	Non-squamous Squamous	29 (72.5) 11 (27.5)
History of brain metastases, n (%)		4 (10.0)
PD-L1 expression, n (%)[a]	<1% 1–49% ≥50%	8 (20.0) 12 (30.0) 20 (50.0)
Baseline ECOG PS, n (%)	0 1	8 (20.0) 32 (80.0)
Smoking history, n (%)	Never Former Current	2 (5.0) 32 (80.0) 6 (15.0)

[a]Per local testing

Safety

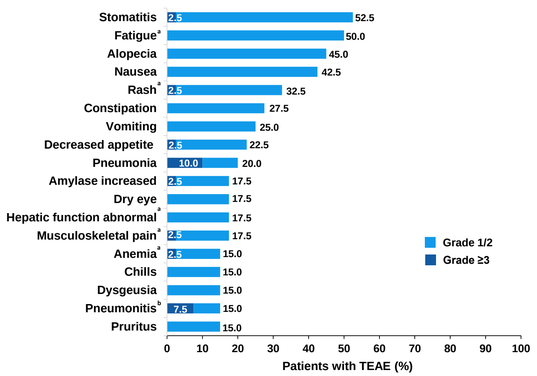
- Overall, there were no treatment-related deaths, and no DLTs were observed.
- Median treatment duration was 5.1 months (range 0.7–18.6).
- Safety is summarized in **Table 2**; 60.0% of patients had grade ≥3 TEAEs.
- The most common TEAEs were stomatitis (52.5%), fatigue (grouped term, 50.0%), alopecia (45.0%) and nausea (42.5%) (**Figure 2**).
- Among AESIs for Dato-DXd, which were predominantly grade 1 or 2:
  - Stomatitis/oral mucositis occurred in 25 (62.5%) patients (grade ≥3: n=1)
  - Ocular surface events occurred in 12 (30.0%) patients (grade ≥3: n=1)
  - Overall, 5 (12.5%) patients had ILD/pneumonitis which was adjudicated as drug-related (grade 2: n=3; grade 3: n=2).

Table 2. Safety summary

	Dato-DXd + rilvegostomig N=40
TEAEs, n (%) Treatment-related	40 (100) 36 (90.0)
Grade ≥3 TEAEs, n (%) Treatment-related	24 (60.0) 10 (25.0)
Serious TEAEs, n (%) Treatment-related	20 (50.0) 6 (15.0)
TEAEs leading to discontinuation of any study drug, n (%) Leading to discontinuation of Dato-DXd Leading to discontinuation of rilvegostomig	9 (22.5) 9 (22.5) 7 (17.5)
TEAEs associated with death,[a] n (%) Treatment-related	6 (15.0) 0

[a]Grade 5 respiratory failure, general physical health deterioration, death, intestinal perforation, sepsis, and cardiac arrest (n=1 each).

Figure 2. TEAEs reported in ≥15% of patients



[a]Grouped preferred terms: anemia (hemoglobin decreased, red blood cell count decreased, anemia, hematocrit decreased), fatigue (fatigue, malaise, asthenia, lethargy), hepatic function abnormal (transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal), musculoskeletal pain (back pain, bone pain, limb discomfort, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, musculoskeletal discomfort, pain in extremity), rash (rash, rash pustular, rash maculo-papular, rash popular, rash macular, rash pruritic); [b]Investigator-reported term

Efficacy

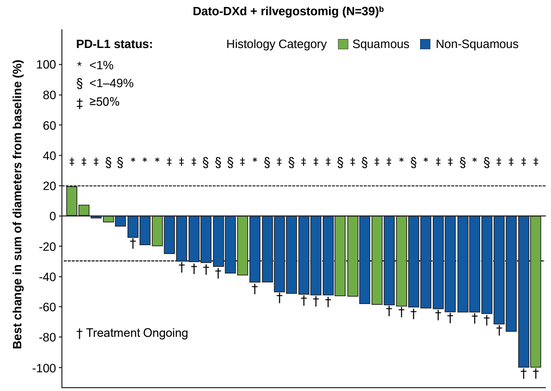
- Response outcomes are summarized in **Table 3**; confirmed ORR for all patients was 57.5%.
- Responses were observed across both squamous and non-squamous histologies (**Table 3**, **Figure 3**, **Figure 4**) and all PD-L1 expression levels (**Figure 3**).
- Notably, highest response rates were observed in patients with both non-squamous disease and high PD-L1 expression (**Figure 3**; non-squamous: PD-L1 <1%, 40.0%; 1-49%, 60.0%; ≥50%, 71.4%).

Table 3. Antitumor activity[a]

	Dato-DXd + rilvegostomig		
	Squamous (n=11)	Non-squamous (n=29)	All (N=40)
Confirmed ORR,[a] % (95% CI)	45.5 (16.7–76.6)	62.1 (42.3–79.3)	57.5 (40.9–73.0)
Median DoR, months (95% CI)	5.7 (2.8–NE)	NE (4.5–NE)	5.8 (4.5–NE)[b]
Best objective response, n (%)			
Complete Response	0	1 (3.4)	1 (2.5)
Partial Response	5 (45.5)	17 (58.6)	22 (55.0)
Stable Disease	4 (36.4)	11 (37.9)	15 (37.5)
Progressive Disease	2 (18.2)	0	2 (5.0)
DCR,[c] % (95% CI)	81.8 (48.2–97.7)	100 (88.1–100)	95.0 (83.1–99.4)

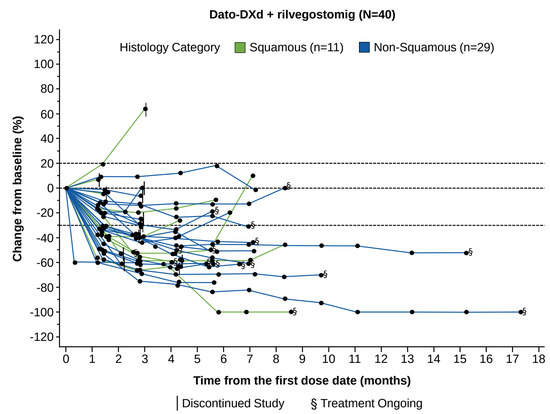
[a]Investigator assessed, per RECIST v1.1; [b]Median DoR data not mature; [c]Defined as patients with CR + PR + SD; SD includes unconfirmed CR/PR or SD ≥5 weeks.

Figure 3. Best change in sum of diameters of target lesions[a]



[a]Investigator assessed per RECIST v1.1.
[b]N=39 as no RECIST evaluation available in one patient due to patient death.

Figure 4. Depth and durability of response[a]



[a]Investigator assessed per RECIST v1.1.

Abbreviations

ADC, antibody-drug conjugate; AESIs, adverse events of special interest; AGAs, actionable genomic alterations; CI, confidence interval; CR, complete response; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DLTs, dose-limiting toxicities; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; Fc-reduced, fragment-crystallizable reduced; IgG1, immunoglobulin G1; ILD, interstitial lung disease; mTPI-2, modified toxicity probability interval-2; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PR, partial response; PS, performance score; RECIST v1.1, response evaluation criteria in solid tumors, version 1.1; SD, stable disease; TEAE, treatment-emergent adverse event; TIGIT, T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain; TPS, tumor proportion score; TROP2, trophoblast cell surface protein 2.

Acknowledgments

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Disclosures

Saiama N. Waqar has acted as a consultant or advisor for AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Gilead, Janssen, and Pfizer; has received research funding (to institution) from SWOG-Clinical Trials Partnership, this funding provides Dr. Waqar with support to oversee the Lung-MAP master protocol and sub study activities; has acted as a principal investigator for AbbVie, Advenchen, Cullinan Pearl, Daiichi Sankyo, Elevation Research & Development LLC, Loxo Oncology, Nuvalent, Ribon, Takeda, and Verastem Inc. For co-author disclosures, please refer to the abstract.

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